



TAMPEREEN TEKNILLINEN YLIOPISTO
TAMPERE UNIVERSITY OF TECHNOLOGY

Antonietta Pepe

**Statistical Shape Analysis in Neuroimaging: Methods,
Challenges, Validation**

Applications to the Study of Brain Asymmetries in Schizophrenia



Julkaisu 1201 • Publication 1201

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Thesis for the degree of Doctor of Science in Technology to be presented with due permission for public examination and criticism in Tietotalo Building, Auditorium TB109, at Tampere University of Technology, on the 25th of April 2014, at 12 noon.

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ISBN 978-952-15-3262-7 (printed)

ISBN 978-952-15-3320-4 (PDF)

ISSN 1459-2045

Abstract

The study of brain shape and its patterns of variations can provide insights into the understanding of normal and pathological brain development and brain degenerative processes. This thesis focuses on the *in vivo* analysis of human brain shape as extracted from three-dimensional magnetic resonance images. Major automatic methods for the analysis of brain shape are discussed particularly focusing on the computation of shape metrics, the subsequent inference procedures, and their applications to the study of brain asymmetries in schizophrenia. Methodological challenges as well as possible biological factors that complicate the analysis of brain shape, and its validation, are also discussed. The contributions of this research work are as it follows.

First, a novel automatic method for the statistical shape analysis of local interhemispheric asymmetries is presented and applied to the study of cerebral structural asymmetries in schizophrenia. The method extracts and analyzes smooth surface representations approximating the gross shape of the outlines of cerebral hemispheres.

Second, a novel and fully automatic image processing framework for the validation of measures of brain asymmetry is proposed. The framework is based on the synthesis of realistic three-dimensional magnetic resonance images with a known asymmetry pattern. It employs a parametric model emulating the normal interhemispheric bending of the human brain while retaining other subject-specific features of brain anatomy. The framework is applied for the quantitative validation of measures of asymmetry in brain tissues' composition as computed by voxel-based morphometry. Particularly, the framework is used to investigate the dependence of voxel-based measures of brain asymmetry on the spatial normalization scheme, template space, and amount of spatial smoothing applied. The developed automatic framework is made available as open-source software.

Third, a novel Simplified Reeb Graph based descriptor of the human striatum is proposed. The effectiveness of such a descriptor is demonstrated for the purposes of automatic registration, decomposition, and comparison of striatal shapes in schizophrenia patients and matched normal controls.

In conclusion, this thesis proposes novel methods for shape representation and analysis within three-dimensional magnetic resonance brain images, an original way for validating these methods, and applies the methods for the study of brain asymmetries in schizophrenia. The impact of this research lies in its potential implications for the development of biomarkers aiming to a better understand-

ing of the brain in normal and pathological conditions, early diagnosis of a number of brain diseases, and development of novel therapeutic strategies for improving the quality of life of affected individuals. In addition, the distribution of simulated data and automatic tools for validation of morphometric measures of brain asymmetry is expected to have a great impact in enabling systematic validation of novel and existing methods for the analysis of brain asymmetries, quantitatively comparing them, and possibly clarifying contradicting findings in the neuroimaging literature of brain lateralizations.

Preface

The research reported in this thesis has been carried out in the Department of Signal Processing of Tampere University of Technology during 2008 – 2013. First of all I would like to express my sincere gratitude to my supervisor Prof. Ulla Ruotsalainen for introducing me to the field of medical imaging and welcoming me into her research group. For this and her precious guidance I am deeply thankful to her. I would like to express my deepest thanks to my supervisor PhD Jussi Tohka for his continuous encouragement, patience, openness to new ideas, and invaluable guidance over the years. Without him this thesis would have never become possible. I wish also to express my gratitude to both my supervisors for believing in me and guiding my research work during the good times, and for their kindness and understanding during the bad times.

I would like to express my gratitude to the co-authors of the published research works for their fertile co-operation. I am especially grateful to PhD Laura Brandolini, Prof. Marco Piastra, PhD Alessandro Foi, MSc Matteo Maggioni and PhD Juha Koikkalainen for the inspiring collaborations, and to PhD Lu Zhao for contributing to guide my first steps as a researcher. I wish to thank Prof. Jarmo Hietala, from the Turku PET center, for providing data and counseling on the neurophysiology. The reviewers of this thesis, Assistant Prof. Natasha Lepore (University of Southern California, USA) and PhD Sylvain Prima (INRIA, France), are gratefully acknowledged for their careful reading and constructive feedback of the manuscript of this thesis. I wish also to thank all the past and present members of the M²oBSI group for the nice working environment, especially my past and present officemates PhD Jukka-Pekka Kauppi, Elaheh Moradi, Juha Pajula, and Uygur Tuna.

From November 2012 to May 2013, I worked at the Laboratory of NeuroImaging (LONI), at University of California Los Angeles (currently at University of Southern California). I am grateful to Prof. Arthur W. Toga for inviting me in his group, and to Assoc. Prof. Ivo Dinov for welcoming me in LONI and helping me with all the practicalities related to the research visit. I wish to thank Assoc. Prof. Yonggang Shi, Assoc. Prof. Eileen Luders, PhD Shantanu Joshi, PhD Junning Li, and other colleagues at LONI for the active discussions on various topic on medical image processing.

The work was financially supported by the Tampere Doctoral Programme in Information Science and Engineering (TISE), Finnish Doctoral Programme in Computational Sciences (FICS), and Academy of Finland. Research grants were received by the Nokia Foundation, the Finnish Cultural Foundation and

the Jenny and Antti Wihuri's Foundation, which are all gratefully acknowledged.

I would like to express my greatest thanks to all my friends that have been close to me during this period. In particular, I am thankful to Raquel Abreu, Roberto Airoidi, Stefano Biancullo, Claudio Brunelli, Oana Cramariuc, Francescoantonio Della Rosa, Cristiano Di Flora, Karim and Angela Di Marzo, Fabio Garzia, Anna Gazzellone, Antonio Ingargiola, Emma Jokinen, Elda Judica, Simona Lohan, Matteo Maggioni, and Paola Vivo for their friendship and nice moments spent together. I would like to thank my brother Giuseppe and his family for being there for me when I needed the most. I am very thankful to my parents, Pasquale and Filomena, for their love and support during my life and studies. I also would like to thank my grandparents, Salvatore and Grazia, and the rest of my amazing family for their love and caring. My last acknowledgment goes to my fiancée' Alberto for his endless love, encouragement, and patience during the years.

Tampere, February 2014

Antonietta Pepe

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List of publications

This thesis is based on the following publications. These are referred to in the text as [Publication-x], where x is a roman numeral.

Publication-I A. Pepe*, L. Brandolini*, M. Piastra, J. Koikkalainen, J. Hietala, and J. Tohka. Simplified Reeb graph as effective shape descriptor for the striatum. In R. R. Paulsen and J. A. Levine editors, *Proc. of MICCAI 2012 Mesh Processing in Medical Image Analysis, Lecture Notes in Computer Science 7599, pages 134 – 146*, Nice, France, 2012 . * Equal contribution.

Publication-II A. Pepe, L. Zhao, J. Tohka, J. Koikkalainen, J. Hietala, U. Ruotsalainen. Automatic statistical shape analysis of local cerebral asymmetry in 3D T1-weighted magnetic resonance images. In R. R. Paulsen and J. A. Levine editors, *Proc. of MICCAI 2011 MeshMed workshop, pages 127 – 134*, Toronto, Canada, 2011.

Publication-III A. Pepe, L. Zhao, J. Koikkalainen, J. Hietala, U. Ruotsalainen, and J. Tohka. Automatic statistical shape analysis of cerebral asymmetry in 3D T1-weighted magnetic resonance images at vertex-level: application to neuroleptic-naïve schizophrenia. *Magnetic Resonance Imaging 31 (5), pages 676 – 687*, 2013.

Publication-IV A. Pepe, and J. Tohka. 3D bending of surfaces and volumes with an application to brain torque modeling. In *1st International Conference of Pattern Recognition Applications and Methods, pages 411 – 418*, Algarve, Portugal, 2012.

Publication-V A. Pepe, I. Dinov, and J. Tohka. An automatic framework for quantitative validation of VBM measures of anatomical brain asymmetry. *Submitted to Neuroimage, under second round of review*.

List of abbreviations

3D	Three-dimensional
4D	Four-dimensional
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BET	Brain Extraction Tool
BFC	Bias Field Corrector
BSE	Brain Surface Extractor
CCA	Canonical Correlation Analysis
CSF	Cerebral Spinal Fluid
DBM	Deformation-Based Morphometry
FDR	False Discovery Rate
FWER	Family-Wise Error Rate
GLM	General Linear Model
GM	Gray Matter
INU	Intensity Non-Uniformity
MANCOVA	Multivariate Analysis of Covariance
MANOVA	Multivariate Analysis of Variance
MC	Monte Carlo
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
N3	Nonparametric Non-uniform intensity Normalization
N4	Improved N3 Bias Correction
RFT	Random Field Theory
ROI	Region Of Interest
SBM	Surface-Based Morphometry
SRG	Simplified Reeb Graph
PCA	Principal Component Analysis
PDM	Point Distribution Model
pFDR	False Discovery Rate
PVE	Partial Volume Effects
TBM	Tensor-Based Morphometry
TFCE	Threshold Free Cluster Enhancement
VBM	Voxel-Based Morphometry
WM	White Matter

Chapter 1

Introduction

During the last few decades, due to the improvements in computing power and increased accessibility of 3D data acquisition systems at relatively low cost, there has been a tremendous growth of studies focusing on the problem of modeling, quantifying, comparing, and classifying the shape of 3D objects. Computer graphics, animation, multimedia, video surveillance, archeology, biology, and medicine are a few examples of possible fields of applications. In this thesis, novel and existing neuroimaging methods for the representation and analysis of brain shapes are presented. Background, motivation, and aims of this research are illustrated in the rest of this chapter.

1.1 Background of the thesis

The research work presented in this thesis focuses on the *in vivo* analysis of human brain shape and its changes as extracted from Magnetic Resonance Imaging (MRI). MRI is a safe and non-invasive medical imaging modality that uses powerful magnetic fields to visualize *in vivo* internal brain structures with high resolution and high contrast between different soft tissues. A number of psychiatric and neurological diseases such as schizophrenia [1,2], Alzheimer's disease [3–5], and dyslexia [6–9], are now known to be linked to neuroanatomical aberrations and their expression can therefore be investigated with MRI. Statistical shape analysis of MRI data can reveal patterns of brain shape abnormalities and thus provide insights into the nature and onsets of these diseases. Beyond providing a means for accurate early diagnosis, the analysis of brain shape can also be used in drug development studies to follow the progression of a disease over time and to track its response to medication, thus leading to better treatment strategies. In addition, in normal conditions, the study of brain

shape can capture the dynamics of brain growth and loss in normal neurodevelopmental and neurodegenerative processes, and pinpoint brain shape changes associated to intense music training [10, 11], orientation [12], meditation [13], juggling [14], as well as demographic, social, genetic, and environmental factors [15, 16]. These studies can provide insights into a better understanding of brain functioning, brain plasticity processes resulting from experiences and learning, and anatomical variations in normal conditions.

1.2 Problem statement and focus of the thesis

In traditional clinical practice, experienced physicians visually examine medical images to guide or support diagnosis. Physicians are able to promptly identify brain structures and to detect possible abnormalities based on qualitative information extracted from head Magnetic Resonance (MR) images and interpreted in light of their extensive experience on normal and pathological appearances of the human brain anatomy. However, experience on the appearance of brain structures is difficult to pass on to new untrained physicians. Moreover, errors due to the subjectivity of image interpretation, duration of the observation task, observer fatigue, distracting factors, and inadequateness of the human experience for a certain dataset under investigation might cause radiological errors or discrepancies [17–20]. Related to this, the naked eye provides only qualitative measures of the geometric properties of objects, whereas accurate, repeatable, and systematic quantitative measures of the brain's shape can only be achieved through automatic quantitative procedures. Automatic and reproducible methods for the analysis of brain shape and of its changes from high resolution 3D MRI data are now available. If properly utilized, these methods can capture subtle and extremely localized brain shape changes that would be difficult to see by the naked eye, or that would otherwise be laborious and time consuming to detect utilizing manual approaches. However, automatic approaches for *in vivo* statistical shape analysis of neuroanatomical structures often face a number of methodological difficulties related to the complexity of the biological problem at hand. Indeed, the human brain shape is complex and highly variable across individuals. In addition, studying the geometric properties of the shapes, partitioning them into classes, or finding similarities and dissimilarities across them are natural tasks for the human visual system but challenging for automatic methods. Automatic methods for statistical shape analysis of brain structures usually follow a precise image processing workflow consisting of the following main steps.

Image acquisition. One or more groups of individuals are selected and typically matched for sex, age, and other factors that could possibly confound the analysis outcome. MRI scans are then acquired for each subject included in the study.

Image quality enhancement. Image quality can be enhanced to improve the accuracy of subsequent automated image processing and analysis.

Segmentation. Brain structures of interest are extracted and separated from the image background.

Shape representation. Quantitative measures of the geometrical properties of the segmented anatomical brain structures are extracted and combined together into a unique descriptor, also referred to as shape descriptor or shape representation. Shape representation is a finite simplified description that captures the relevant geometrical properties of an object for which an index can be built and comparisons can be performed efficiently. Meshes and sets of biologically relevant landmarks are natural and popular examples of shape representation in neuroimaging applications.

Alignment. Shape representations of the studied anatomical brain structures are typically aligned to each other to separate relevant shape information from sources of meaningless shape variations such as brain size, position, and orientation.

Statistical analysis. Statistical shape analysis of aligned brain structures is performed between- or within-groups. The between-groups analysis is used, for instance, to detect possible effects of a disease in a group of patients as compared to normal controls. The within-group analysis is used, for example, to provide information on possible trends in the data.

Different automatic methods for the statistical brain shape analysis have been proposed in the MRI literature, nearly all based on the major steps outlined above. The primary interest of this thesis lies in the study of automatic image processing methods for the analysis of between-group differences in brain shapes from 3D MRI data. Special focus is given to aspects regarding the computation of shape metrics, the subsequent inference procedures, the methodological limitations of automatic methods for shape analysis in neuroimaging applications, as well as to the need for validation of these automatic methods.

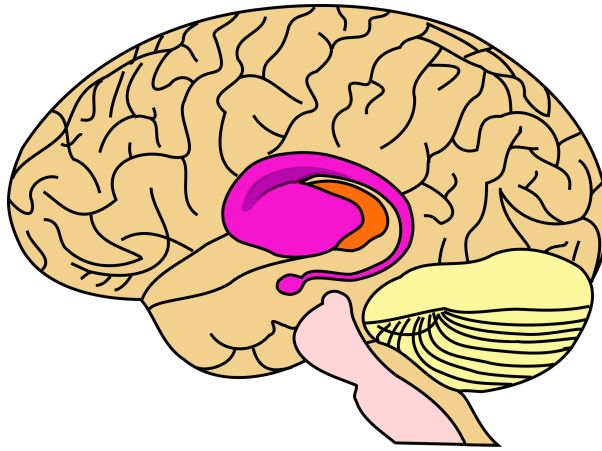


Figure 1.1: Striatum and the human brain. Striatum is depicted in purple, thalamus in orange. Adapted from <http://en.wikipedia.org/wiki/Striatum> (author: John Henkel).

1.3 Motivating examples

The motivations of this thesis are explained in the following Sections 1.3.1 and 1.3.2, which give examples of *in vivo* studies of patterns of neuroanatomical abnormalities in schizophrenia. These examples also serve as introduction to the problems to which the methods developed in this thesis are applied, namely the study of striatal shapes and the study of cerebral inter-hemispheric asymmetries in schizophrenia and normal population.

1.3.1 Striatal shape and schizophrenia

The striatum is a deep and highly innervated group of nuclei in the brain, and the primary afferent of nerves from the cerebral cortex and the thalamus [21] (see Fig. 1). In addition to learning, attention, memory, motivation, reward, and addiction, the striatum is implicated in cognitive functions and in motor processes [22–24]. The study of the striatum is of high interest in schizophrenia since cognitive and motor symptoms have been often reported in neuroleptic-naïve patients presenting schizophrenia [25–27]. Several, but not all, MRI studies have found larger striatal volumes in patients with schizophrenia [1]. Also, there is evidence that antipsychotic medication [28–30], and atypical antipsychotic drugs to a smaller degree [31], can affect striatal anatomy. Thus, the effect of medication is a confounding factor in the studies of the striatum in schizophrenia and studies on neuroleptic-naïve patients are needed to evaluate possible neuroanatomical correlates of the disease. However, non-medicated subjects affected by schizophrenia are hard to find due to the fact that treatment

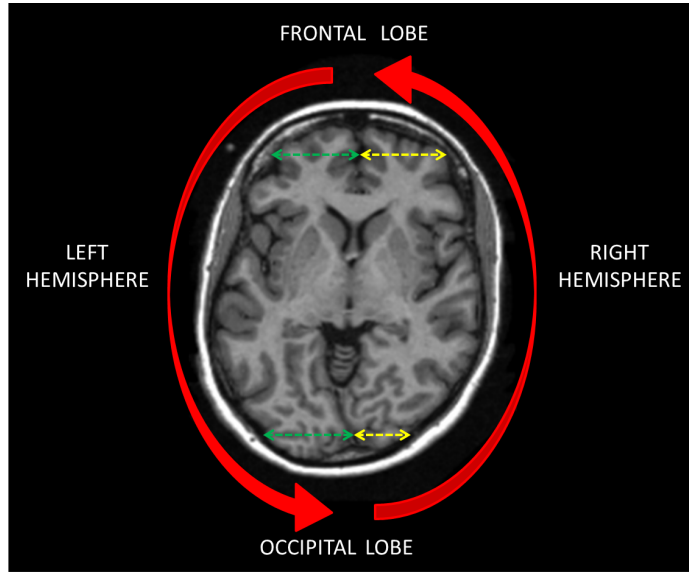


Figure 1.2: Right-frontal left-occipital *petalia* and Yakovlevian torque. Yellow and green arrows depict the width of the left and right cerebral hemispheres, respectively. Red arrows highlight the direction of the Yakovlevian torque.

with anti-neuroleptic medications is typically started right after the diagnosis. Moreover, the inconsistency in measurement techniques [32] and the dynamics of the disease further confound the association with diagnosis [33]. In addition, recent neuroimaging findings suggest that the link between anatomy, function, and diseases of the human brain is typically highly complex and involves anatomical changes in multiple locations of the brain. This could partially explain the inconsistencies in the neuroimaging literature and suggests that traditional volumetric analysis of manually delineated brain structures might be overly simplistic, especially for brain regions having complex anatomy such as the human striatum.

1.3.2 Brain asymmetries and schizophrenia

The anatomical asymmetry between the two hemispheres of the human brain, typically referred to as interhemispheric, bilateral, or left-right asymmetry, is an important developmental phenomenon which arises already in fetal life [34] and then evolves during childhood and adulthood [35,36]. *In vivo* neuroimaging studies have consistently found several patterns of brain structural interhemispheric asymmetries and there are strong indications of correlations between structural brain lateralizations and age, gender, evolutionary, hereditary, hormonal, and pathological factors, see [15] or [37] for a review. Links have also

been found between anatomical interhemispheric asymmetries and asymmetrical behavioral traits such as hand and foot preference [38–41], auditory perception [42], and language production [43–47]. Abnormal left-occipital right-frontal *petalia* [48] and reduced or reversed Yakovlevian torque [49] are two of the most consistently reported abnormal patterns of brain interhemispheric asymmetry in schizophrenia [50], dyslexia [51], learning disabilities [52], and autism [51]. Brain *petalia* consists in the greater protrusion of the right hemisphere over the left one in the frontal lobe, and the greater protrusion of the left hemisphere over the right one in the occipital lobe [15] (see Fig. 1.2). Yakovlevian torque, also referred to as Yakovlevian anti-clockwise torque or simply as brain torque, consists in the rightward bending of the interhemispheric fissure due to the aforementioned frontal protrusion of the right hemisphere and the occipital protrusion of the left hemisphere [15] (see Fig. 1.2). The study of brain *petalia* and the related Yakovlevian torque is important for the understanding of the neuroanatomical bases of schizophrenia. It has been suggested that the Yakovlevian torque might be an important anatomical basis for development of asymmetric brain functions, and that disturbed Yakovlevian torque in schizophrenia might reflect the failure to establish left hemisphere dominance, thus leading to the disease [2, 53–55]. The relation between schizophrenia and interhemispheric anatomical asymmetries has been reported by many but not all [56, 57] studies. Inconsistent findings have often been attributed to different MRI scanning settings and image properties, disparate sample sizes, inconsistent sample inclusion criteria, disease heterogeneity (first-episode versus chronic schizophrenia), and medications heterogeneity (neuroleptic-naïve versus medicated subjects) [9, 58–61]. Inconsistencies in the literature have also been attributed to non-reproducible methodological practices, different image processing, and different measurement criteria that capture different aspects of brain asymmetry and are thus difficult to relate one to the other [40, 58–63]. Additionally, intrinsic limitations of volume measurements prevent the detection of subtle and localized abnormalities in brain shape [24, 61].

1.4 Challenges

The examples reported in Section 1.3 highlight the difficulties that neuroscientists encounter in making reliable inferences from neuroanatomical findings. Although there are neuroimaging studies confirming relations between structural brain findings with cognitive deficits, social impairments, demographic factors, and a number of psychiatric and neurological diseases, it is often difficult to assess how reliable these findings are, how they are affected by ex-

periment settings, imaging characteristics, and methods employed, and how different measures of brain changes relate to each other. In the following, the specific challenges partially addressed by this thesis are described.

Methodological and computational challenges related to large sample sizes.

Large databases of multidimensional (3D, sometimes also 4D) and high resolution MRI data are now becoming increasingly available due to the joint efforts of multiple medical centers and universities (see [64–66]). This calls for the need of automatic and computationally efficient methods for image processing and analysis in neuroimaging applications.

Methodological challenges related to small sample sizes. When no brain MRI data is freely available for a particular population of interest, qualifying individuals need to be scanned and carefully screened for confounding factors such as age and gender. MRI data acquisition still remains a relatively costly and time consuming process. There are also particular study groups, such as first-episode neuroleptic-naïve subjects affected by schizophrenia described in Section 1.3, that are extremely rare to find. Identifying subtle brain shape changes from relatively small sample sizes represents a challenge for many methods due to the low statistical detection power. This calls for proper attention to the design of automatic brain shape analysis methods and the statistical procedures implemented therein.

Biological Challenges. The shape of the human brain is complex and highly variable across individuals. If applied for diagnostic applications, automated image processing methods need to be able to detect pathological changes while accounting for the normal inter-subject variability in brain shapes, and for the effects of other confounding factors.

Validation of quantitative methods. Although there exist a number of methods for automatic statistical shape analysis of brain structures, there are still important challenges in quantitatively validating brain morphometric methods and results. This is due to the lack of simulated brain images, and the lack of ground truths for comprehensive and systematic validation of automatic methods for brain shape analysis.

1.5 Objectives and structure of the thesis

In this thesis, novel and existing methods for the representation and analysis of brain's shape, as extracted from 3D brain MR images, are reviewed and investigated. Special emphasis is given to the challenges related to the development of such methods and their validation. Applications to the study of straital

shape and brain shape asymmetries in schizophrenia and normal populations are also presented. The rest of the thesis is organized as follows. Chapter 2 presents background information on statistical shape analysis and reviews the major shape descriptors used in computer graphic and neuroimaging applications. In Chapter 3, a general image processing pipeline for the statistical shape analysis of brain anatomy from head 3D MRI data is illustrated, along with possible methodological limitations and open challenges. In Chapter 4, automatic methods for the statistical shape analysis of the whole brain are reviewed and compared. Chapter 5 summarizes the publications in which the research of this thesis is reported, and the author's contribution to the published work. Particularly, a novel Simplified Reeb Graph based descriptor for the human striatum is presented and its effectiveness is demonstrated for the purposes of automatic registration, decomposition, and comparison of striatal shapes in a small sample of neuroleptic naïve-subjects diagnosed with schizophrenia and matched normal controls. In addition, a novel automatic algorithm for the statistical shape analysis of interhemispheric asymmetry in cerebral surfaces is introduced and tested in a small sample of neuroleptic naïve-subjects diagnosed with schizophrenia as compared to matched normal controls. The algorithm is fully automatic and can thus be applied to large 3D-MRI data, while also being able to cope with small sample sizes as we have demonstrated in our publications. Furthermore, a novel framework for validation of statistical shape methods for the analysis of brain asymmetries is introduced. It employs a parametric model emulating the left-occipital right-frontal *petalia* and related Yakovlevian torque as often found in normal subjects. Finally, concluding remarks and open challenges are discussed in Chapter 6.

Chapter 2

Elements of statistical shape analysis

Statistical shape analysis of brain structures is an important tool in computational neuroanatomy for studying how brain anatomy is affected by demographic, genetic, pathologic, and cognitive neuropsychological factors, and for monitoring the progression over time of different pathologies and treatment responses. This chapter provides a brief overview on the concept of shape, shape representation, shape analysis, statistical shape analysis, and morphometry. Landmarks are used in this chapter to provide examples and illustrate concepts.

2.1 Shape

Shape is defined as the geometrical information that remains when global location, scale, and rotational effects are removed when studying an object [67,68]. Shape is therefore invariant to similarity transformations [69].

The size and shape, or form, is defined as the geometrical information that remains when location and rotational effects are removed when studying an object, while the geometrical information about size is retained [67,68].

2.2 Shape descriptors

In order to be able to compare the shape of objects, each object must be represented using a fixed number of homologous measurements, called shape descriptor or shape representation. Shape representation is a finite summary description of the shape which carries the most important information while being

easy to be handled.

Landmarks. Landmarks are one of the most common shape descriptors. Landmarks consist of a set of pre-defined points on the object boundary that can be reliably estimated from an image. The work in [68] defines a landmark as a point of correspondence on each object that matches within and between populations. A landmark can either be (1) an anatomical landmark, if the point has a specific biological or structural significance; (2) a mathematical landmark, if the point is defined according to some mathematical or geometrical property; (3) or a pseudo-landmark, if the point is artificially constructed to connect other types of landmarks [68].

Meshes. A polygonal mesh is a collection of vertices and edges that can be used to represent a surface. Triangular meshes are one of most popular format of shape representation for 3D objects in medical imaging applications.

Parametric descriptors. In brain imaging applications, biological or mathematical landmarks are not always available or easy to identify due to the smoothness of brain structures, inter-subject variability, and image noise. Alternatively, boundary coordinates of simply connected 3D objects can be decomposed in a set of basis functions such as spherical harmonics [70,71]. Spherical harmonics based descriptors were first introduced to represent radial or stellar surfaces, and have been then extended [72] to describe arbitrarily shaped 3D objects (simply connected) with protrusions and intrusions [73]. Spherical harmonic based descriptors have the advantage of requiring only very few landmarks (typically used to register the contours) and to produce an orthogonal basis in which objects' shapes can be easily compared [73].

Medial descriptors. A medial axis, or skeleton, of a shape is defined as the set of centers and radii of all the maximal inscribed balls. Unlike skeletons, Reeb graphs [74] are shape descriptors for closed and connected surfaces that have been proved to be robust to small surface perturbations [75]. The definition of a Reeb graph is based on the concept of Morse function [76, 77], and it can be intuitively thought as describing the connectivity relation between the level lines of the Morse function on the surface. As a remarkable property of Reeb graphs, they preserve the topology of closed and connected surfaces meaning that the number of loops of the Reeb graph is equal to the genus of the surface [78]. [Publication-I] describes the implementation of a discrete variant of Reeb graph for closed triangular meshes.

2.3 Statistical shape analysis

Statistical shape analysis, also typically referred to as morphometry, is a relatively new branch of mathematics studying the shapes and shape changes of (geometric or biological) objects.

In [68, 79], features are constructed by taking the coordinates of landmarks after first optimally aligning the objects using Procrustes superimposition. Procrustes analysis is a process which matches configurations of landmarks by using least squares to minimize the mean squared Euclidean distance between them, thus removing the effects of location, rotation, and scale.

The analysis of shape configurations based on landmark data has led to the formulation of the distribution of shapes in shape space and their applications for examining shape differences between populations [68, 69, 79]. The idea behind the theory is that, if different shapes are represented with a same number of landmarks consistently placed along their contour, each shape corresponds then to a different element of the shape space, and the quantization of the shape differences is achieved via a metric on this space. However, it is often difficult to estimate the optimal number and position of landmarks needed to properly represent an object. Moreover, a relatively big number of landmarks is needed to accurately represent complex shapes, but the problem of dimensionality increases proportionally to the number of landmarks used.

In [80, 81], a predefined finite number of anatomical landmarks is selected in corresponding analogue biological positions in each subject being studied. Once superimposed using Procrustes method, a Point Distribution Models (PDM) is build to model the variation of the coordinates of the labeled landmarks, and their relative positions is then analyzed via Principal Component Analysis (PCA).

Chapter 3

Elements of MR image processing and analysis

This chapter describes the major image processing and analysis steps involved in a typical quantitative morphometric study of brain anatomy based on MRI data. These steps aim at improving image quality, segmenting the brain structures of interest, aligning them, and extracting quantitative morphometric measures that are then spatially smoothed and statistically analyzed within or between groups. A generic automatic workflow for the statistical shape analysis of brain anatomy from MRI data is depicted in Fig. 3.1 and explained in the rest of this chapter.

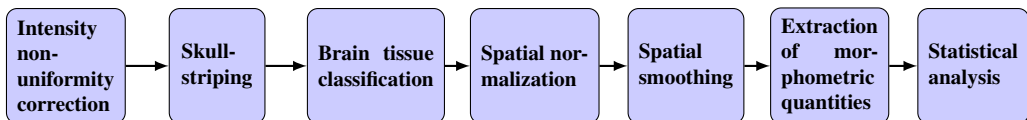


Figure 3.1: A generic automatic workflow in a typical quantitative morphometric study of brain anatomy based on MRI data. Notice how these steps can be arranged differently depending on the particular method implementation and purpose of the study.

3.1 Image pre-processing

Intensity non-uniformity correction. Intensity non-uniformity (INU) is an unavoidable artifact of MRI consisting in slow and smooth variations in signal intensities throughout the image due to imperfections in the radio-frequency coils, acquisition pulse sequence of the MR imaging device, and patient induced interactions [82–84] (see Fig. 3.2, panels a-c). INU has no anatomical

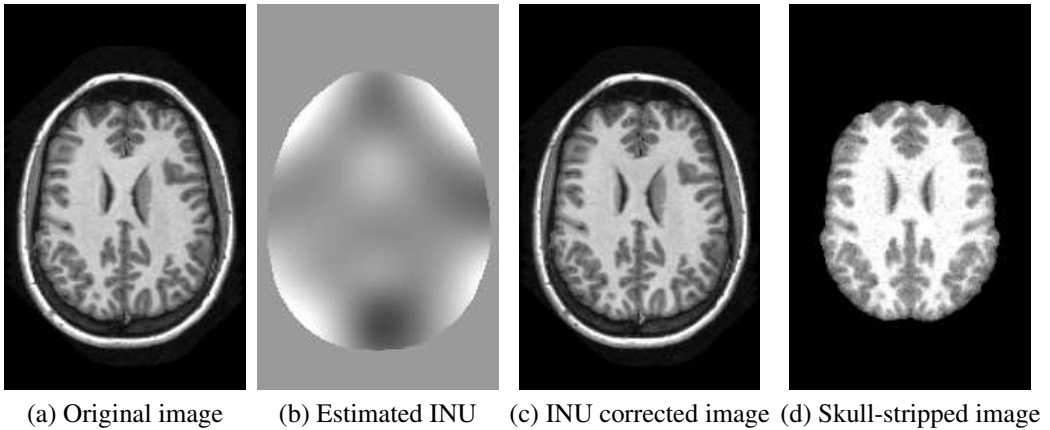


Figure 3.2: INU correction and skull-stripping.

relevance and, if not corrected, it can affect the accuracy of the subsequent automatic image processing and morphometric quantitative analysis.

A number of image processing algorithms have been developed to compensate for both machine and patient-induced low-frequency spatial intensity variations in MRI based on the assumption that INU variations are spatially smooth across the image, and that an ideal INU corrected image is piecewise constant [83]. Solutions to the INU correction problem have been proposed based on modelling of the INU as a smooth surface using basis functions [85], or by filtering INU corrupted images in spatial [86] or transformed [87] domains. Other approaches combine the INU correction with the brain tissues segmentation problem (discussed in the remainder of this Section) using statistical methods [88–90]. The BFC (Bias Field Corrector) [91], the N3 (Nonparametric Non-uniform intensity Normalization) [92], and the N4 (Improved N3 Bias Correction) [93] are largely used and well validated algorithms for INU correction [33]. For a review and a quantitative validation on algorithms for INU correction see [83,94] and [95], respectively.

Skull stripping. Quantitative morphometric studies of the brain typically require to isolate brain from non-brain tissues such as skull, scalp, eyeballs, and skin (see Fig. 3.2, panel d). This process is referred to as skull-stripping, brain extraction, or whole-brain segmentation.

Available automatic skull-stripping methods are based on the contrast and intensity values in MRI data. Some of the automatic methods for skull-stripping, named region-based methods, approach the brain extraction problem by trying to identify connected regions based on image intensity via hard thresholding,

clustering, watershed, and morphological filtering (for more details see [96,97] and references therein). There are then boundary-based methods that approach the brain extraction problem by trying to detect the boundary between brain and non-brain tissues based on intensity gradient information using surface-based models [97], local optimization of the intensity gradient [98], or a combination of intensity thresholding methods with edge detection methods [99]. BSE (Brain Surface Extractor) [99] and BET (Brain Extraction Tool) [97] are two largely popular algorithms for skull stripping [100].

As quantitatively demonstrated in references [100, 101] and discussed in [96], the accuracy of automatic methods for skull-stripping is typically variable with the image and neuroanatomical characteristics of the particular data-set being processed. Region-based methods are typically sensitive to image noise, contrast, INU, and they suffer from oversegmentation [96]. Boundary-based methods are typically sensitive to the quality of initialization and scanning parameters [96]. For this reason, in order to ensure acceptable accuracy of the skull-stripping and subsequent brain morphometric analyses, it might be necessary to perform image quality checks, as well as manual tuning of the skull-stripping methods' parameters and manual editing on the processed images [96, 102].

Brain tissue classification. Brain tissue classification is a step often implemented in automatic brain morphometric methods. It refers to the problem of segmenting brain images into its three major brain compartments, namely the gray matter (GM), the white matter (WM), and the cerebro spinal fluid (CSF).

First solutions to the brain segmentation problem were based on hard thresholding [103]. However, these methods are particularly sensitive to image noise, contrast, and Partial Volume Effects (PVE). PVE refers to the existence in a voxel of a mixture of tissue types and background (such as the mixture GM/WM, GM/CSF, or CSF/background) due to finite image resolution. This complicates and often impedes an accurate brain segmentation if performed exclusively based on image intensity values. Alternative approaches have been proposed based on statistical classification algorithms [104], clustering based algorithms [105], and PVE estimation [106]. A review on brain segmentation is reported in [107].

3.2 Brain image registration

Spatial normalization. Brain image registration, also referred to as brain image alignment, consists in the process of mapping a given brain image into a

target brain image. If the target brain is conform to a standard reference space, the term spatial normalization is generally preferred.

In many computational morphometric applications, spatial normalization is performed to 'convert' brain data from the original coordinate system, typically referred as *native space*, into a standard reference space. This establishes an approximate anatomical correspondence among brain structures and allows for meaningful comparisons among different brains. To this purpose, linear (low dimensional) spatial normalization transformations are typically used to compensate for size, orientation, and global shape differences between brains. Rigid (translation + rotation), affine (translation + rotation + stretches + shears) or in general any 3D linear registration can be described as:

$$X' = TX \quad (3.1)$$

where $X = [x, y, z, 1]^T$ and $X' = [x', y', z', 1]^T$ denote the 4D coordinate vectors in the original and transformed space, respectively, and where T is the following 4 x 4 transformation matrix in homogeneous coordinate system:

$$T = \begin{pmatrix} a_{11} & a_{12} & a_{13} & t_1 \\ a_{21} & a_{22} & a_{23} & t_2 \\ a_{31} & a_{32} & a_{33} & t_3 \\ 0 & 0 & 0 & 1 \end{pmatrix}. \quad (3.2)$$

In other morphometric methods, the spatial normalization is used to warp brain images to match as closely as possible a standard reference brain, and the obtained spatial normalization transformations are used as a basis for the quantification of the brain shape differences. To this aim, affine registration followed by a smooth and highly nonlinear (high dimensional) spatial normalization techniques are typically used. A nonlinear 3D registration can be represented as:

$$d(X) = X + u(X) \quad (3.3)$$

where $X = [x, y, z]^T$ is again the 3D coordinate vector in the original space, $d(X)$ is a 3D deformation vector at each position X , and where $u(X) = [u_1, u_2, u_3]^T$ can be interpreted as the displacement vector field measuring the relative movement of point X . The displacement vector $u(X)$ gives a measure of the local translation from each original location X to the transformed space, and as such it only captures the first-order morphological variability [108].

An alternative interpretation for the displacement vector field $u(X)$ can be done in terms of basis functions, such as the polynomial transformation function from

the original coordinates X , as well as basis functions based on discrete cosine transform and spline basis functions [33, 108].

From the deformation field $d(X)$, the Jacobian matrix $J(X)$ can be defined as the gradient of the field $d(X)$:

$$J = \frac{\partial d}{\partial X^T} = I + \nabla u = I + \frac{\partial u}{\partial X^T} = I + \begin{pmatrix} \frac{\partial u_1}{\partial x_1} & \frac{\partial u_1}{\partial x_2} & \frac{\partial u_1}{\partial x_3} \\ \frac{\partial u_2}{\partial x_1} & \frac{\partial u_2}{\partial x_2} & \frac{\partial u_2}{\partial x_3} \\ \frac{\partial u_3}{\partial x_1} & \frac{\partial u_3}{\partial x_2} & \frac{\partial u_3}{\partial x_3} \end{pmatrix} \quad (3.4)$$

where I is the 3 x3 identity matrix and ∇u is the displacement gradient matrix. The 9 components of the gradient matrix ∇u are called displacement tensor and measure the second order morphological variability [108]. The determinant of the Jacobian of the deformation field at each location unit cube represents the volume change introduced by the registration transformation at that location [108, 109] (see Section 4.2.4).

Optimal transformation parameters are estimated as the ones providing the best alignment among brain images according to a certain criterion or cost function. Next, the estimated transformation parameters are applied to the source brain image that is thus resampled in the reference space.

Reference Space. Currently, the two most widely used reference spaces (also referred to as standard or stereotactic space/atlas/template) for reporting results in brain morphometric studies are the population average atlas of 152 young adults normal brains [110] collected from the International Consortium for Brain Mapping, and the population average atlas of 305 young adults normal brains [111] collected from the Montreal Neurological Institute. Other customized (domain-specific) templates have been also proposed to best represent the anatomy of specific populations such as children [112], Alzheimer's patients [113, 114], and other specific clinical populations [33]. Study-specific templates directly obtained from the data under investigation are also possible [115]. A critical review on the potentialities and challenges associated to the creation of population- and study-specific average atlases is exhaustively presented in [116].

Algorithms for spatial normalization. One of the most widely used spatial normalization technique for within-modality registration is based on adjusting the parameters of the spatial normalization transformation by optimization of a measure of intensity similarity across individual images [102, 108]. Highly non-linear image registration methods have been developed based on elastic deformation and fluid dynamics models (typically by optimization of a measure of similarity) [114, 117–123], or based on the more recent diffeomorphic

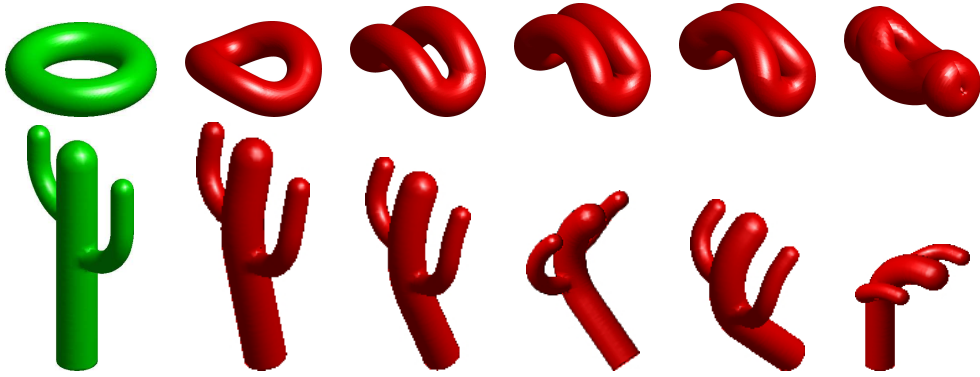


Figure 3.3: Bending deformations of a parametric (torus, first row, original surface is depicted in green, deformed surfaces obtained for different parameters of the model are depicted in red color) and polygonal surface (cactus, second row, original surface is depicted in green, deformed surfaces obtained for different parameters of the model are depicted in red color).

framework [124–129]. The estimation of transformation parameters might use regularization to prevent unreasonable warps [130], and multiscale optimization to speed up convergence and avoid local minima [131] (see also [102]). Exhaustive reviews on non-linear registration in neuroimaging applications are reported in [123, 126, 132–135], and the comparative quantitative reviews in [123] and [135]. Quantitative analysis of the impact of spatial normalization and template space selection in the outcome of certain morphometric methods is reported in [115, 136, 137] and [Publication-V].

Other applications of registration. There are alternative applications in neuroimaging applications that are based on brain image registration. One of this is to provide segmentation by registering a labeled reference brain into an unlabelled one. Another application allows parametric shape modifications by deforming the underlying space in which the object is embedded. This can be done, regardless of the particular shape representation employed, to apply scaling, translation, rotation, and affine transformations. Space deformations can also be used to apply more sophisticated parametric remapping of the space, such as the global linear bending proposed in [138], and the rescaled adaptive Global Linear Bending deformation (see Fig. 3.3) that was introduced and applied in [Publication- IV and V] to mimic the left-occipital right-frontal *petalia* and the related rightward bending of the interhemispheric fissure.

3.3 Spatial smoothing

In morphometric applications, spatial smoothing is usually performed before the statistical analysis via convolution of brain image (e.g. gray values) data with a 3D Gaussian kernel of fixed width (although other kernel smoothing methods are also possible [139]). Spatial smoothing partially compensates for the noise introduced during image acquisition and processing, and it smooths out the inter-subject variability remaining from the spatial normalization [108, 140, 141]. Spatial smoothing is important for brain morphometric applications because it can increase the statistical sensitivity and statistical power of a test, and thus reveal morphological patterns that would otherwise be covered by anatomical noise [108, 139]. Spatial smoothing can also make data more normally distributed, and in turn increase the validity of parametric tests [108, 140, 141]. On the other hand, spatial smoothing blurs fine details and reduces the accuracy in the localization of the detected brain morphometric changes toward regions of lower variance [141]. Therefore, as discussed in [108, 139] and qualitatively demonstrated in [Publication-V], the amount of spatial smoothing modulates the intensity and spatial extent of the detections, and remains a crucial stage of the morphometric method design.

3.4 Statistical analysis

General linear model. Depending on the particular morphometric method used (see Chapter 4), a quantitative measure of brain shape is extracted and it is statistically analyzed within or between groups. A general linear model (GLM) is typically fitted to the data at each brain location and a map of p -values¹ is obtained. GLM identifies brain locations where a statistically significant change or effect occurred while accounting for nuisance covariates. GLM can be used for one-sample or two-sample t -tests, as well as for the analysis of more complex interactions between various effects of interest via canonical correlation analysis (CCA), analysis of variance (ANOVA), analysis of covariance (ANCOVA), or the multivariate analysis of variance (MANOVA) [102, 142].

Multiple comparisons correction. In several automated quantitative morphometric methods, statistical analysis is performed via massively univariate approaches (see Chapter 4). As an example, consider the case of a voxel-level

¹In classical hypothesis testing, a p -value expresses the evidence against the null hypothesis (typically of no effect or difference) for a test-statistic; in other words it refers to the chance under the null hypothesis of observing a test statistic at least as large as the one observed [102].

hypothesis testing performed on a brain image of size $100 \times 100 \times 100$ voxels with $1 \times 1 \times 1 \text{ mm}^3$ voxel size. If an hypothesis test with a 'per test' error margin $\alpha = 0.05$ is performed at each of the 10^6 voxels independently, there will be approximately 5000 voxels that should be expected to be significant ($p\text{-value} \leq \alpha$) due to chance alone when there is no effect. These false detections, typically referred to also as false positives or type I errors, need to be corrected before the significance of the overall map can be assessed [33]. Algorithms have been proposed to control for the multiplicity of tests based on two possible distinct measures of false positive risk: the family-wise error rate (FWER) that is defined as the chance of one or more false positives, or the false discovery rate (FDR), a less stringent measure of false positive risk that is defined as the expected proportion of false positives among detections [102, 143, 144].

In brain morphometric studies, test statistics in adjacent locations are typically highly correlated. The Bonferroni procedure controls the FWER at level α_{tot} by rejecting the null hypothesis of each test at level $\alpha = \alpha_{tot}/N$, where N is the number of tests, and α_{tot} is the total error margin of the multiple comparisons corrected test. Bonferroni is a valid procedure for FWER correction but it is overly conservative for spatially correlated tests, thus leading to a large proportion of false negatives (type II errors).

Random Field Theory (RFT) [145, 146] is an alternative method for the multiple comparisons error correction that controls the FWER while accounting for spatially correlated test statistics. RFT estimates the distribution of the maximum test statistic while adapting to the intrinsic smoothness of the data [144, 147, 148]. RFT makes several strong assumptions on the distribution and correlation structure of the data, that do not always hold true in practical applications [149, 150]. In order to better approximate a continuous random process, RFT requires the data to be sufficiently smooth, thus reducing the spatial resolution of the analysis outcomes (see Section 3.3). Although more lenient than the Bonferroni correction, RFT has been demonstrated to be overly conservative, especially for data with low smoothness and relatively small sample sizes [102, 144, 151]. RFT is the method of choice for multiple comparisons error correction in [Publication-V].

Monte Carlo simulation (MC) [152–154] is another method for multiple comparisons error correction that controls the FWER and accounts for spatially correlated test statistics. Under the null hypothesis of no significant differences between groups, MC estimates basic features of the data such as its smoothness. Using an estimate of the smoothness of the real data, Gaussian data is then simulated and used to generate surrogate statistic images under the null hypothesis [102]. The observed test statistics can be finally compared to the simulated

distributions, and used to control the FWER. MC assumes the Gaussianity and estimates the smoothness of the data just like RFT does; however, MC has the advantage over RFT of not depending on the accuracy of RFT approximations at the cost of a more computationally expensive procedure [102, 144].

Permutation test [155–158] is an alternative method to correct for multiple comparisons that provides exact control of the FWER and accounts for spatially correlated test statistics. The test calculates empirical null distributions by repeatedly permuting the data with respect to groups labels under the null hypothesis of no significant difference between groups, thus avoiding strong assumptions about the spatial autocorrelation of the process [102]. In practice, subjects are shuffled with respect to groups labels. Upon the random assignment of each subject to a specific group, the resulting empirical distribution is calculated, and an overall threshold for correcting the p -values of the test is calculated from the proportion of random maps that have an effect as or more extreme than that of the map obtained for the true grouping [33]. This approach overcomes the conservativeness of RFT, and, due to its weak assumptions, can be used for nonstandard scenarios as we have done in [Publication-II and III]. However permutation methods are computationally intensive [33, 102].

Alternative solutions to the problem of multiple comparisons in brain morphometric applications have been proposed based on more lenient FDR measure of error [143, 159, 160] and on the positive FDR (pFDR) [161, 162].

Voxel- and cluster-based inference. Voxel- and cluster-based inference are two different methods for assessing the significance of an effect of interest in massively univariate tests while controlling for the false positives. In voxel-based inference the significance of an effect is established based on its intensity using a single threshold. On the other hand, in cluster-based inference, clusters are defined as contiguous regions whose intensity exceeds a predefined cluster-defining threshold u_c , and significant clusters are then detected as the ones whose spatial extension exceed a critical size threshold. In general, while voxel-based tests are more powerful for high intensity effects, cluster-based tests are more powerful for detecting spatially extended effects [163, 164]. In addition, while voxel-based tests provide the most spatially specific form of inference, cluster-based tests take into account the spatial information in the image although they lack of spatial specificity [102]. An important aspect of cluster-based inference is how to define the cluster-defining threshold u_c and the amount of spatial smoothing to be applied. Indeed, depending on u_c and on the smoothing performed, the results of cluster-based inference can change considerably. Some practical guidelines on the choice of the u_c threshold and

spatial smoothing to be used in cluster-based inference have been given in [165] for different degrees of freedom. A threshold free cluster enhancement (TFCE) algorithm has been proposed [166] to ameliorate the dependence of cluster-based inference on the u_c selection.

Different implementations of voxel- and cluster-based inferences have been proposed based on RFT [167], permutations [158, 168], and MC simulations [154]. Combined (hybrid) methods to control the multiple comparisons errors have been proposed based on RFT [164] and permutations [155, 165], and have been reported to be sensitive when both voxel- and cluster-based statistics are marginally significant but not significant *per se* [155], and when only one but not the other statistic is significant [165]. However, combined methods have been extensively validated only for simulated t-images [165, 169], simulated Gaussian images [169], and more recently also for simulated nonstationary volumetric images [165].

Chapter 4

Automatic brain morphometry

Brain morphometry, intended as the detection and quantitative analysis of human brain shape and its changes, is an important tool in computational neuroimaging. Brain morphometry can be used to detect and characterize neuroanatomical differences among populations, to study how patterns of neuroanatomical shapes' variations are affected by demographic, genetic, pathologic, and neuropsychological factors, and for monitoring the progression of different pathologies and treatment responses over time [142]. This chapter describes major automatic morphometric methods for the analysis of the whole brain, focusing on aspects regarding the computation of shape metrics, the subsequent inference procedures, and their applications in neuroimaging studies of 3D MRI data. For the sake of completeness, traditional volumetric approaches are also reviewed. The case study in this chapter deals with the study of brain interhemispheric neuroanatomical asymmetries in schizophrenia versus normal population.

4.1 Traditional brain volumetry

In the earliest *in vivo* brain morphometric studies, a few specific regions-of-interest (ROI) were manually delineated in each studied individual and their size quantified via measurements of volume, length, area, or mass. In these measurement techniques, each segmented ROI structure was typically normalized to take into account of possible different brain sizes and then its variations were analyzed across subjects [170–172] or in time [173]. Such process typically required an a priori hypothesis on one or a few particular brain structures, and the manual segmentation of those [109]. When analysing a large number of brains, acquiring volumetric measures for several brain structures is an extremely time-

consuming task if done manually, and it is typically biased from subjective criteria in the manual ROI delineation. As a consequence, most volumetric studies need to rely on small numbers of samples and few ROI manually delineated on only a few MRI slices [174]. Moreover, traditional brain volumetric studies were typically restricted to the analysis of hippocampi, brain ventricles, and other brain structures having higher contrast than neighboring structures, thus being easier to be manually or semi-automatically delineated [142]. One additional limitation of these traditional morphometric studies was related to the fact that they were based on volume or other simple measurements of size, such as area, distances, or ratios of distances. While these simple measurements of size provide some indication of normal variation and anomaly, they allow only summary comparisons of the geometric properties of the objects and do not capture the entire complexity of anatomical shape, nor are capable of detecting the locations where differences occur [24, 140, 175–179].

4.2 Modern automated brain morphometry

Automatic morphometric methods for the analysis of the whole brain anatomy have been recently proposed to overcome most of the problems described in the previous Section. These modern automated methods typically do not require the segmentation of ROI and as such can be applied to more generic situations, where specific *a priori* hypotheses are not available. In addition, they propose more sophisticated automated procedures, better suited for the analysis of the complex brain shape and to be used for high dimensional databases.

Modern automated brain morphometry methods can be classified into two macro categories:

- those methods examining the individual local brain shape differences remaining after that macroscopic individual differences in position, size, orientation, and global shape have been filtered out;
- those methods analysing the individual macroscopic brain shape differences in terms of the deformation fields adopted for non-rigidly aligning (warping) each brain to match closely to a same reference space [109, 141].

In the former category, which includes Surface-Based Morphometry (SBM) and Voxel-Based Morphometry (VBM), smooth deformation fields are used to establish a global anatomical correspondence among brain structures, and thus to

allow region-by-region comparisons among different brains. In the latter category, which includes Deformation-Based Morphometry (DBM) and Tensor-Based Morphometry (TBM), high dimensional deformation fields describing the spatial normalization are analyzed to detect differences in cross-subject studies, or temporal changes in longitudinal studies. In the remainder of this chapter the key ideas of these modern brain morphometric methods are described.

4.2.1 Surface-Based Morphometry

Surface-Based Morphometry (SBM) [180–183] is a fully automated method for the vertex-level analysis of the shape of structural boundaries between different tissue types after macroscopic differences in gross anatomy, position, size and orientation have been discounted. In SBM, a structure of interest is segmented and a surface representation of the studied boundary is created. Automatic surface extraction algorithms have been introduced for sub-cortical structures such as hippocampus [184] and corpus callosum [185], for detailed cortex [91, 186–188], and for overall cortex approximations [106] as we have done in [Publication-II, and III]. Manual or semi-automatic methods are also possible. After the surface extraction, a regular mesh structure is imposed on all individual shapes being studied and point-to-point correspondence is established. Anatomical correspondence between geometrical shapes at vertex-level is achieved by compensating for pose, size, and global brain shape differences across subjects' surfaces. To achieve or improve the point-to-point correspondence accuracy, a somehow challenging and computationally costly process (see for example [189, 190]), remeshing can also be performed. Once all structures are normalized to a standard reference space, an average anatomical mesh is generated by averaging corresponding surface points of the surface representations of individual shapes. Next, one or multiple indexes of brain morphology are computed based on the geometrical properties of the extracted surfaces, they are typically smoothed and then analyzed across subjects. These shape indices can be used for generating maps of shape variability [191, 192].

4.2.2 Voxel-Based Morphometry

Voxel-Based Morphometry (VBM) is a fully automated whole brain method for voxel-level analysis of local brain tissue composition after individual differences in gross anatomy, position, orientation, and size have been discounted [140–142, 175, 193, 194]. In VBM, brain images are first segmented into GM, WM, and CSF tissue compartments typically using image intensity and a priori

knowledge on the likely spatial distribution of brain tissues via Bayesian methods [91, 142, 195]. Tissue classification can be performed either jointly with the correction for INU [195], or after it (as in [Publication-V]). Next, individual tissue maps are spatially normalized into a tissue specific template image in a common reference space. Spatial normalization is achieved by compensating for position, orientation, size, and global shape differences between individual brains images via affine spatial normalization followed by a low-dimensional non-linear spatial normalization. The aim of spatial normalization is to establish a coarse macroscopic anatomical correspondence of brain structures while preserving local shape differences [140, 175]. Once spatially normalized, individual partitioned tissue maps can be modulated. Modulation involves the multiplication of the spatially normalized tissue-specific images by the Jacobian determinant of the deformation field introduced by the spatial normalization [140, 142, 196]. In practice, modulation converts the concentration of brain segments (relative amounts of a certain tissue type in a voxel - density) into actual volume (absolute amounts of that same tissue type in a voxel - mass) by compensating for the relative volume changes introduced by the spatial normalization in a certain partitioned tissue type at each voxel [142, 197]. After spatial normalization and possible modulation, the same voxel location in each image corresponds roughly to the same brain structure and can be thus analyzed at voxel-level. The first step of the statistical analysis in VBM consists in the spatial smoothing by convolution with an isotropic Gaussian kernel or box filter. Spatial smoothing reduces the residual anatomical inter-subject variability remaining from the imperfect spatial normalization, thus increasing the sensitivity of detections [33, 115]. By the central limit theorem, spatial smoothing also increases the normality of the data and it is thus used in VBM studies to improve the validity of parametric tests that are used in the statistical analysis [140, 141] (see also Section 3.3). Smoothed brain tissue maps are statistically analyzed via massively univariate standard parametric procedures computed at each voxel by fitting a GLM to the data. This identifies regions of statistically significant changes or effects in tissues' composition (concentration or volume), typically after discounting for confounding factors (see [33], [141] and references therein). Results are finally corrected for the multiple comparisons problem using nonparametric procedures [155–158] or Gaussian Random Field Theory [198, 199], and presented as statistical parametric maps.

4.2.3 Deformation-Based Morphometry

Deformation-Based Morphometry (DBM) is a fully automated whole brain method that characterizes macroscopic anatomical differences in the relative

positions of brain structures from deformation fields that non-linearly map one brain to another [142, 200–204]. In DBM, individual brain anatomy (brain images or surfaces) are typically accurately warped into a reference neuroanatomical template using high-dimensional non-linear registration. The obtained deformation fields describe the spatial transformations required to match each brain to a template, and as such they capture the differences between source and target brains by characterizing their spatial position differences at corresponding locations [108, 109, 142].

As reviewed in [108] and [33], DBM analysis can be performed differently depending on how the deformation field $d(X)$ is represented.

In one approach to DBM analysis, deformation fields $d(X)$ are represented as a set of basis function coefficients parameterizing the non-linear warping of source to template brain [204, 205]. Deformation fields can also be represented in terms of coefficients of the functions that warping algorithms use to represent the deformation fields, such as the discrete cosine transform [206], polynomials [207], spherical harmonics [180–182], or the eigenfunctions of self-adjoint differential operators [208]. If a basis function representation of the deformation field is employed, basis functions can be analyzed via spectral methods [208], Riemannian shape manifolds [209], or with multivariate methods such as canonical variate analysis [206] (see [33, 108, 210] for more details).

A completely different approach to DBM analysis computes statistics on the deformation field $d(X)$ required to align each individual brain with the reference space at each brain location X . In this approach, affine components of the deformation fields $d(X) = X + u(X)$ are factored out and a statistical model is constructed based on the displacement vector $u(X)$:

$$u(X) = \mu(X) + \sigma^{1/2}(X)\epsilon(X) \quad (4.1)$$

where $\mu(X)$ is the mean deformation vector, $\epsilon(X)$ is the error vector that is assumed to be independent and identically distributed, $\sigma(X)$ is a non-stationary, anisotropic covariance tensor field estimated from the mapping, and $\sigma^{1/2}(X)$ denotes the square root of $\sigma(X)$ and it is defined as a 3×3 symmetric positive-definite covariance matrix representing the correlation between deformation components [33, 108, 146, 202]. Next, statistical analysis is performed on features that are directly extracted from $\mu(X)$, such as its intensity and principal directions (eigenvectors) [33, 108, 202]. Between-group shape differences are analyzed via standard multivariate statistical methods such as Hotellings T^2 test, MANCOVA (multivariate analysis of covariance), or CCA (canonical correlation analysis). It is worth mentioning that before constructing the test-statistic,

an important task is to perform image smoothing, which is necessary to guarantee the Gaussianity of $\mu(X)$.

Alternatively, since deformation fields are a rich source of morphometric data, statistics can be performed to generate an atlas. The significance of deviations from this atlas can be assessed to provide criteria for detection of abnormal anatomy after being corrected for the multiple comparisons problem [33].

4.2.4 Tensor-Based Morphometry

Tensor-Based Morphometry (TBM) is a fully automated whole brain method that characterizes differences in the local shape of brain structures from gradients of deformation fields that non-linearly map one brain to another [132, 142, 211–213]. In TBM, subjects' brains (images or surfaces) are non-linearly warped into a neuroanatomical reference space. Next, the tensor fields derived from the spatial derivatives of the registration transformation are computed at each voxel and used to identify regions of spatial between-groups shape differences, or to identify locations of temporal intra-subject shape differences in longitudinal studies. The displacement tensor $\nabla u(X)$ associated with a certain deformation field $d(X)$ at point X of the original anatomy is a 3x3 matrix describing the principal directions of the deformation field at that point (see [108] and Chapter 3). The local Jacobian determinant $\det \mathbf{J}$ of the deformation field $d(X)$ is often used to summarize the information on local volume effects produced by the deformation $d(X)$ that aligns two shapes at point X . Particularly, there is local shrinkage if $0 < \det \mathbf{J} < 1$, there is a local expansion if $\det \mathbf{J} > 1$, there is no volume change if $\mathbf{J} = 1$, there is a biologically impossible deformation (folding) if $\det \mathbf{J} < 0$, and there is tearing if $\det \mathbf{J} \gg 1$ and approaches infinity [174, 178]. Dilation rates, contraction rates, and magnitude of the principal direction of local volumetric changes (tissue growth or loss) can be also computed from the Jacobian matrix of the deformation field $d(X)$, or from the eigenvectors of the displacement tensor $\nabla u(X)$ at each point X . Volume dilatation is the first-order approximation of the Jacobian determinant with respect to the unit cube (i.e. $\det \mathbf{J} - 1$) [108, 201]. Significant differences in deformation fields across subjects or between-groups are then assessed via multivariate statistical analysis. Results are commonly presented in the form of maps of statistically significant effects or differences after correction for the multiple comparisons problem.

Alternatively, the resulting Jacobian determinant images, also called Jacobian maps, may be aligned to an average group template and statistically analyzed using massive univariate voxel-level statistics [33, 200, 211, 214, 215].

Notice that the displacement vector $u(X)$ used in DBM (see Eq. 3.3) gives a measure of the local translation at each voxel as compared to the original position before the deformation field was applied, and as such it only captures the first-order morphological variability. On the other hand, the Jacobian determinant $\det \mathbf{J}$ used in TBM approximates the unit-cube volume dilation and it is thus better suited for studying patterns of brain growth [108].

Notice also that DBM and TBM can be applied to brain surfaces in addition to brain volumes, see for example Moo K. Chung's work on surface DBM for localizing the cortical regions of growth and loss in longitudinal brain images of children and adolescents, and the Yalin Wang's work on surface multivariate TBM on parametric surface models for diagnostic classification applications [216, 217]. Surface DBM and surface TBM have been separated from the SBM category to better fit the methods classification given in the beginning of Section 4.2.

4.3 Applications in the study of brain asymmetry

As discussed in [Publication-II and III], SBM based methods have been used to study the shape asymmetry [202] and shape variability [218] of gyral and sulcal patterns on detailed cortical surfaces, and patterns of interhemispheric asymmetries in cortical thickness [219] and cortical morphology [183] at matching homologous locations between the hemispheres. [220] proposed a novel asymmetry index of cortical thickness, while [221] used the position vertex asymmetry and the surface area asymmetry on hemisphere mid-surfaces as measures for the cerebral cortex morphology.

As reviewed in [Publication-III and V], VBM based methods have been employed to measure voxel-level interhemispheric differences in tissue density [222] and tissue volume [140, 177] from large samples of 3D-MR images. In these studies, first the original brain images were reflected with respect to their planes of symmetry, and then differences between the original and flipped brain images were computed and analyzed voxel-wise.

[223] developed a DBM based method to quantify regional volume differences between homologous structures in the two hemispheres using a 3D tool for non-rigid registration of the MR brain images and their symmetric versions flipped across the symmetry plane in the image. In [224], individual left and right hemispheric images were first warped into representative template images, and then, the differences in magnitude and variance of the obtained deformation parameters were used as a basis for the assessment of cortical asymmetry.

In [225], asymmetry in WM growth patterns in childhood-onset schizophrenia was analyzed using TBM.

4.4 Comparisons

The aforementioned methods (SBM, VBM, DBM and TBM) find a common ground in the fact that the entire brain can be accurately examined with an objective and repeatable procedure that does not involve manual interventions. Each of the described methods has its pros and cons. The choice of the appropriate approach must rely on the expected type of brain structural difference or effect, and on the computational resources available. A comparison of the different morphometric methods is presented in Table 4.1.

Additionally, the described methods measure different aspects of the morphological changes. DBM measures the relative displacement of brain structures and indicates the principal direction of brain growth, also known as first order morphological variability. DBM can be therefore used to identify brain structures that have translated to different positions as a consequence of the spatial normalization. If applied to 3D brain images, DBM studies the relative position of two particular voxels, before and after the deformation, but does not give information on the local shapes and thus on the local growth or shrinkage [108, 142, 226]. The analysis of local growth or shrinkage is important in capturing the dynamics of brain changes in longitudinal studies of normal and pathological conditions, including normal neurodevelopment and aging, as well as in detecting pattern of growth of brain tumors or the progression of atrophic processes in Alzheimer's disease. Local growth and loss can be exploited in full only with second order derivatives extracted from the deformation field as done in TBM. In addition, since tensors have the advantage over displacement vectors of being invariant to translational shifts, TBM can distinguish intrinsic volumetric changes from translational shifts in anatomy. Translational shifts of a certain brain structure can be caused by, e.g., disease induced changes in a neighbor structure [33]. These patterns of changes cannot be distinguished neither by DBM approaches, nor by VBM, unless perfect alignment of brain structures is available [33, 227]. VBM and SBM provide instead localized measures of shape changes at corresponding brain locations.

With a regard to VBM, the interpretation of significance of the detected brain changes should take into account not only the accuracy of the image pre-processing, especially the accuracy of segmentation and spatial normalization, but also the template space used, the amount of non-stationary residual vari-

	SBM	VBM	DBM	TBM
Main references	[180–183]	[140, 142, 175, 193, 194]	[142, 200–204]	[132, 142, 211–213]
Main idea	Statistical vertex-level analysis of measures computed in homologous locations of surface representations after they have been aligned one to another	Statistical voxel-level analysis of brain tissues composition (density or volume) computed in homologous locations after brain images have been coarsely aligned one to another	Statistical analysis of measures directly derived from deformation fields introduced by the non-linear spatial normalization employed to map a source brain into a reference one	Statistical analysis of measures derived from gradients of deformation fields introduced by the non-linear spatial normalization employed to map a source brain into a reference one
What it measures	Local shape changes in boundaries (e.g. thickness)	Local changes in tissue composition (density or volume)	Local displacement change	Local volume change
Statistical analysis	Vertex-level analysis	Voxel-level analysis	Analysis on the intensity or principal direction of translational shifts in brain structures	Analysis on the intensity (e.g. rate of growth) and direction of patterns of brain growth or loss in brain structures
Applied to	Surface	Volume	Volume or surface	Volume or surface
Segmentation	Required	Required	Not required	Not required
Spatial normalization	Low dimensional	Low dimensional	High dimensional	High dimensional
Computational cost	Relatively low	Relatively low	Relatively high	Relatively high

Table 4.1: Comparisons of methods. Notice how VBM analyses local brain shape differences remaining after the coarse registration of individual brain volumes to match a reference brain volume. Similarly, SBM analyzes local brain shape differences remaining after the registration of individual brain surfaces to match a reference brain surface. On the other hand, in surface DBM and TBM, macroscopic shape differences are extracted from the deformation fields used for warping individual brain surfaces to match closely a reference brain surface.

ance in the data, and the kernel size used for the Gaussian spatial smoothing [115, 136, 137, 140, 175, 228–230]. This limitation of VBM has been discussed and quantified in [Publication-V] for different alignment schemes, different template images, with and without modulation, and with progressively increasing kernel sizes of the spatial smoothing.

It is also worth mentioning that the methods discussed are substantially different from each other in terms of computational cost. In particular, while DBM and TBM require computationally expensive estimation of high dimensional

deformation fields, VBM and SBM only require the estimation of smooth and low-dimensional deformation field thus representing a simpler and more affordable approach [141].

Chapter 5

Summary of publications

This chapter summarizes the main contributions of the peer-reviewed publications in which the research of this thesis is reported, and the contributions of the author to the published work.

5.1 Summary of publications

[Publication-I] A. Pepe*, L. Brandolini*, M. Piastra, J. Koikkalainen, J. Hietala, and J. Tohka. *Simplified Reeb graph as effective shape descriptor for the striatum*. In R. R. Paulsen and J. A. Levine editors, *Proc. of MICCAI 2012 Mesh Processing in Medical Image Analysis, Lecture Notes in Computer Science* 7599, pages 134 – 146, Nice, France, 2012. * *Equal contribution*.

[Publication-I] presents a novel image and mesh processing pipeline that uses Simplified Reeb Graphs (SRG) as an effective shape descriptor for closed triangle meshes of the human striatum. The main contribution of the work lies in demonstrating that SRG can be effectively used as a robust descriptor of the striatal shape that is stable with respect to mesh density and small local variations on the mesh. Additionally, the study explores the effectiveness of such a descriptor for the purpose of automatic inter-subject mesh registration, automatic mesh decomposition, and for between-groups shape comparisons. The proposed pipeline is tested on 3D MRI data collected from neuroleptic-naïve patients presenting schizophrenia and matched controls. Experimental results show that the accuracy of the SRG-based registration of striatal meshes quantitatively outperforms the accuracy of surface-based registration. In addition, the automatic mesh decomposition obtained as a direct result of the SRG extraction is demonstrated to be a valid alternative to the laborious manual sub-segmentation of the human striatum. Preliminary results indicate that,

despite its compactness, SRG is sensitive to shape variations and can be used for between-groups shape comparisons.

[Publication-II] A. Pepe, L. Zhao, J. Tohka, J. Koikkalainen, J. Hietala, U. Ruotsalainen. *Automatic statistical shape analysis of local cerebral asymmetry in 3D T1-weighted magnetic resonance images. In R. R. Paulsen and J. A. Levine editors, Proc. of MICCAI 2011 MeshMed workshop, pages 127 – 134, Toronto, Canada, 2011.*

[Publication-II] presents a novel automatic image processing method for local (vertex-level) statistical shape analysis of cerebral hemispheric surface asymmetry from 3D head MRI data. The method extracts smooth mesh representations approximating the gross shape of the cerebral hemispheres' outlines. As additional contribution of this work, the developed method is tested on a relatively small sample of first-episode neuroleptic-naïve schizophrenic subjects. Experimental results demonstrate that the method, despite the relatively small sample sizes and high inter-subject variability in position, extent, and morphology of the cortical patterns, is able to detect various patterns of statistically significant asymmetries in the male schizophrenic subjects which survive the multiple comparisons correction.

[Publication-III] A. Pepe, L. Zhao, J. Koikkalainen, J. Hietala, U. Ruotsalainen, and J. Tohka. *Automatic statistical shape analysis of cerebral asymmetry in 3D T1-weighted magnetic resonance images at vertex-level: application to neuroleptic-naïve schizophrenia. Magnetic Resonance Imaging 31 (5), pages 676– 687, 2013.*

[Publication-III] describes extensions of the method introduced in [Publication-II] for the analysis of between-groups local brain shape asymmetries. The method is applied to study the overall cerebral hemispheric shape asymmetries in a relatively small sample of neuroleptic-naïve schizophrenics as compared to matched normal controls. Experimental results reveal various patterns of significant main effects of the diagnosis at the frontal and temporal lobes, the latter being often linked to the cognitive, auditory, and memory deficits in schizophrenia. The findings of this research work are in agreement with previous well-established studies on brain asymmetries supporting the hypothesis of a neuroanatomical etiology of schizophrenia and interpreting the disease as either a neurodevelopmental or a neurodegenerative disorder. In conclusion, the findings of this study add evidence to the possible involvement of multiple abnormal neuroanatomical asymmetries in the pathogenesis of schizophrenia.

The outcomes of this study are also an important indicator for the sensitivity of the proposed method.

[Publication-IV] A. Pepe, and J. Tohka. *3D bending of surfaces and volumes with an application to brain torque modeling. In 1st International Conference of Pattern Recognition Applications and Methods, pages 411 – 418, Algarve, Portugal, 2012.*

[Publication-IV] presents a novel space deformation model to approximate the bending deformation in 3D volumes and surfaces. It extends an existing model for linear bending deformation to allow more flexible transformations of the space and to include constraints on the deformation while maintaining the simplicity of the model. Experimental results demonstrate the increased modeling capabilities of the proposed bending deformation when compared to previous models for local bending. The above model is further extended to mimic the interhemispheric bending of the human brain. Additionally, a novel automatic image processing pipeline is proposed for the generation of simulated databases with a realistic and parametrically known asymmetry pattern to be used for validation of voxel- and surface-based morphometry. Due to the simplicity of the model and to the automatism of the whole image processing pipeline, the latter can be used for generating large validation databases.

[Publication-V] A. Pepe, I. Dinov, and J. Tohka. *An automatic framework for quantitative validation of VBM measures of anatomical brain asymmetry. Submitted to Neuroimage, under second round of review.*

[Publication-V] presents a fully automatic framework for the quantitative validation of brain tissues' asymmetries as measured by VBM from 3D MRI data. The framework utilizes and extends the work in [Publication-IV]. Based on each brain MRI, a pair of simulated MR images with a known and realistic pattern of interhemispheric asymmetry is generated while retaining other subject-specific features of brain anatomy. As the second contribution of this work, a ground truth image of brain asymmetry values is generated using parametric modeling. Additionally, an optimized VBM analysis is implemented and applied to validate the detected asymmetries in brain tissues' composition against the computed ground truth asymmetry values. The sensitivity and specificity of the detected VBM asymmetries in brain tissues' composition are also investigated in relation to the spatial normalization scheme, modulation, template space, and amount of spatial smoothing applied. The developed automatic framework, along with the simulated data generated and the correspond-

ing ground truth values of brain asymmetry in stereotaxic space, will be made available as open-source software and material to promote further quantitative studies aiming at the validation of new and existing voxel- and surface-based morphometric methods for the analysis of neuroanatomical asymmetries.

5.2 Author's contribution to the publications

The author of this thesis is the first author and main contributor of all the publications collected in this research work. In [Publication-I], the first authorship was shared with PhD L. Brandolini from University of Pavia, Italy. Particularly, [Publication-I] is the result of a joint effort of the author and the co-authors. The author is responsible for the design of the method, implementation of the inter-subject mesh registration, assessment of the mesh registration accuracy, between-groups shape comparisons, and manuscript preparation. The first co-author L. Brandolini was responsible for the design and implementation of the SRG as well as manuscript preparation. As the first author of [Publication-II, III, IV, and V], the author of this thesis was responsible for the methods implementation, execution of experiments, manuscript preparation, and the management of the research effort that led to the published methods and results. All co-authors listed in each publication have contributed to the research work giving valuable comments to the developed methods and discussing new ideas that led to improvements of the published methods and results. Data used in [Publication-I, II, III, and IV] was provided by the Turku PET Center, Turku, Finland. Data used in [Publication-I] was partially pre-processed by co-author PhD J. Koikkalainen, from the VTT Technical Research Centre of Finland, Tampere, Finland. Data used in [Publication-II] was partially pre-processed by co-author PhD L. Zhao, from the McConnell Brain Imaging Center, Montréal, Canada (formerly Tampere University of Technology, Tampere, Finland). [Publication-III and V] are based on previous publications and original ideas by the author. Each publication is the fruit of original work carried out by the author and supervised by PhD J. Tohka, and Prof. U. Ruotsalainen. Particularly, co-author and supervisor J. Tohka actively contributed to the original ideas, method design, and management of the research work in all the publications collected in this research work.

Chapter 6

Discussion

The study of brain shape and its variations can be used as a powerful tool to uncover patterns of brain changes in normal and pathological conditions, possibly leading to a better understanding of brain dynamics and functioning, more accurate diagnosis, and better treatment strategies. However, automated methods for statistical shape analysis come with various methodological limitations. The combination of these limitations together with the intrinsic complexity of the biological problem leads to important research challenges.

In the work described in this thesis, novel automatic methods for shape representation and analysis within brain MRI are presented and applied for the study of brain asymmetries in schizophrenia. A novel automatic method for the statistical shape analysis of asymmetries in the outlines of cerebral hemispheres (surfaces) is presented along with an original way for validating voxel-based and surface-based measures of anatomical brain shape asymmetry. The need for developing fully automatic methods for statistical shape analysis is discussed in this thesis in relation to the increased availability of large high resolution 3D MRI data-sets, and thus to the need of analyzing these data-sets in a fast, inexpensive, and highly reproducible manner. In addition, a general automatic image processing pipeline for the analysis of brain shape is described while highlighting the major open challenges related to biological aspects, study design inconsistencies, and methodological limitations.

With a reference to the aforementioned biological challenges, human brain structures have complex shapes and they are subject to a certain level of normal inter-subject variability that can confound the morphometric analysis of the brain. This is especially evident in case of small sample sizes, as the ones described in [Publications-II and III], where low effect sizes and low power of the statistical tests might hide important between-group differences. In addition,

shape changes can be subtle and thus hard to detect.

With a reference to the aforementioned inaccuracies due to the study design, it is worth to mention that inconsistencies in the participant inclusion criteria, disease heterogeneity, medications heterogeneity, and disparate scanning settings (thus variable imaging characteristics) can also confound the analysis and hide biologically important effects as discussed in [Publication-I, II, III and V].

Concerning the aforementioned methodological challenges, it is worth mentioning that automatic methods for statistical shape analysis of brain anatomy are composed of long workflows typically including INU correction, skull-stripping, brain segmentation, spatial normalization, and spatial smoothing. Each of these steps represents a source of potential errors that can propagate through further steps of the image processing workflow and thus to the analysis outcomes. Particularly, it has been criticized that image processing errors, especially the segmentation and spatial normalization stages, as well as the inappropriate selection of spatial smoothing kernel sizes, can lead to false detections. These issues have been discussed in many studies [137, 141, 224, 227, 229], and quantitatively demonstrated in a few more ones, such as in [115, 136] and in [Publication-V]. Furthermore, the use of customized templates typically produces superior sensitivity of brain morphometric methods [115, 137]. This is related to the fact that if *ad-hoc* templates are used, the variability introduced by the spatial normalization will be reduced and thus the power of detection will increase. In addition, it has been criticized that linear statistical approaches used in certain morphometric methods for the analysis of brain shape are biased toward effects that are highly localized in space and of linear nature, rather than effects that are spatially complex even if with higher magnitude [229]. Since brain structures are believed to have highly non-linear characteristics, and since inter-relations among different brain structures should be expected as well, fully multivariate statistical approaches have been thought to be better suited for the analysis of brain shape [229]. However, multivariate results can not be communicated and interpreted quite as easily compared to (massively) univariate results, and they might require more intensive computations [231]. Among the different methods for quantifying and comparing brain shapes, some methods are better suited to detect subtle effects that are spread across relatively large brain regions, while other methods are better suited for highly localized effects. The choice of the brain morphometric method for the particular problem at hand should take into account the expected effect and the computational resources available.

A parallel line of research considered in [Publication-I] demonstrated the potentialities of compact shape descriptors as a possible alternative to more local-

ized and computationally intensive description of the shape for the purpose of between-groups shape comparisons.

In conclusion, this thesis proposes novel automatic methods for representation and analysis of brain shapes within 3D MRI, and describes their applications to the study of structural brain asymmetries in a small sample of neuroleptic-naïve patients diagnosed with schizophrenia and matched controls. The impact of this research lies in its potential implications for the development of biomarkers aiming to a better understanding of brain anatomy and functioning, normal and pathological brain shape variability and dynamics, early diagnosis of mental diseases, and development of better treatment strategies for improving the quality of life of affected individuals. In addition, the distribution of simulated brain MRI data and of an automatic framework for validation of morphometric measures of brain asymmetry is expected to have a great impact in enabling systematic and comprehensive quantitative validation of novel and existing methods for the analysis of brain asymmetries, and possibly clarifying contradicting findings in the neuroimaging literature of brain lateralizations.

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ISBN 978-952-15-3262-7
ISSN 1459-2045